Idiopathic Normal Pressure Hydrocephalus Pathogenesis

- Causal associations between gut microbiota, metabolites, and idiopathic normal pressure hydrocephalus: a two-sample Mendelian randomization study
- Clinical Features and Diagnosis of Normal Pressure Hydrocephalus
- Single-cell elderly blood-CSF atlas implicates peripherally influenced immune dysregulation in normal pressure hydrocephalus
- Cerebrospinal Fluid Biomarkers in Idiopathic Normal Pressure Hydrocephalus: Bibliometric Analysis and Literature Review
- Anosmia and Upper Limb Rigidity-A Potential Phenotype of Idiopathic Normal Pressure Hydrocephalus with Cerebrospinal Fluid alpha-Synuclein Seeds
- Implications of the glymphatic system in the pathogenesis of normal pressure hydrocephalus: an illustrated scoping review
- The impact of perioperative aspirin utilization on postoperative hemorrhagic complications in idiopathic normal pressure hydrocephalus: a single-center retrospective analysis
- Beyond early motor response: Longitudinal cognitive and gait assessments after extended lumbar drainage in normal pressure hydrocephalus

---

The pathogenesis of idiopathic normal pressure hydrocephalus (iNPH) remain unclear.

There are currently no idiopathic normal pressure hydrocephalus disease genes or biomarkers. A systematic analysis of familial idiopathic normal pressure hydrocephalus could aid in clinical diagnosis, prognosis, and treatment stratification, and elucidate disease patho-etiology. In a 2-part analysis, Greenberg et al. reviewed literature-based evidence for inheritance of idiopathic normal pressure hydrocephalus in 22 pedigrees, and then present a novel case series of 8 familial idiopathic normal pressure hydrocephalus patients. For the case series, demographics, familial history, pre- and post-operative symptoms, and cortical pathology were collected. All novel familial idiopathic normal pressure hydrocephalus patients exhibited improvement following shunt treatment and absence of neurodegenerative cortical pathology (amyloid-beta and hyperphosphorylated tau), in contrast to many sporadic cases of idiopathic normal pressure hydrocephalus with variable clinical responses. Analysis of the 30 total familial idiopathic normal pressure hydrocephalus cases reported herein is highly suggestive of an autosomal dominant mechanism of inheritance. This largest-ever presentation of multiply affected idiopathic normal pressure hydrocephalus pedigrees provides strong evidence for Mendelian inheritance and autosomal dominant transmission of an idiopathic normal pressure hydrocephalus trait in a subset of patients that positively respond to shunting and lack neurodegenerative pathology. Genomic investigation of these families may identify the first bona fide idiopathic normal pressure hydrocephalus disease gene [1)]

CSF dynamics show two major abnormalities: a pulsatile increase in CSF pressure and increased outflow resistance.

Ventricular enlargement with near normalization of hydrostatic pressure takes place but the pathophysiology involved in these phenomena remains highly disputed [2].

Although the exact pathogenesis of NPH is unknown, many possible causes have been postulated, including cerebral ischemia.

Studies have demonstrated that periventricular blood flow and cerebrovascular autoregulation are reduced.

It is also thought that biomechanical changes, such as the combination of tissue distortion caused by ventricular dilation, CSF and interstitial fluid stasis, and impaired autoregulation may result in failure of drainage of neurotoxic compounds such as Amyloid beta.

Increased CSF stroke volume through the aqueduct has also been demonstrated in the NPH population despite normal CSF pressures. The reaction of the cerebral mantle to all or some of these processes is poorly understood. It is thought that white matter tract connections serving the cortex could be disrupted in a variety of ways, including disconnection, swelling, stretching, and compression. Therefore, it is possible that some types of disruption may be more tolerable (i.e., more reversible) than others.

Only a few studies have seized the opportunity to reevaluate the theories of pathogenesis of NPH using developments in imaging techniques.

The disorders of Alzheimer disease, vascular dementia and normal pressure hydrocephalus are all causes of dementia in the elderly population. It is often the case that it is clinically very difficult to tell these diseases apart. All three forms of dementia share the same risk factors, which for the most part are vascular risk factors. Bateman proposes that there is an underlying vascular pathophysiology behind these conditions, which is related to the strength of the pulse waves induced in the craniospinal cavity by the arterial vascular tree. It is proposed the manifestation of the dementia in any one patient is dependant on the way that the pulsations interact with the brain and its venous and perivascular drainage. This interaction is predominately dependant on the compliance of the craniospinal cavity and the chronicity of the increased pulse wave stress [3].

1)
Greenberg ABW, Mehta NH, Mekbib KY, Kiziltug E, Smith HR, Hyman BT, Chan D, Curry WT Jr, Arnold SE, Frosch MP, Duy PQ, Kahle KT. Cases of familial idiopathic normal pressure hydrocephalus implicate genetic factors in disease pathogenesis. Cereb Cortex. 2023 Oct 7:bhad374. doi: 10.1093/cercor/bhad374. Epub ahead of print. PMID: 37814356.
2)
Qvarlander S, Lundkvist B, Koskinen LO, Malm J, Eklund A. Pulsatility in CSF dynamics: pathophysiology of idiopathic normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 2013 Jul;84(7):735-41. doi: 10.1136/jnnp-2012-302924. Epub 2013 Feb 13. PubMed PMID: 23408066.
3)
Bateman GA. Pulse wave encephalopathy: a spectrum hypothesis incorporating Alzheimer's disease, vascular dementia and normal pressure hydrocephalus. Med Hypotheses. 2004;62(2):182-7. PubMed PMID: 14962623.